Sleepwalking, REM Sleep Behaviour Disorder and Overlap Parasomnia in Patients with Parkinson's Disease

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Abstract: Background/Aims: In a questionnaire survey, we identified 36 (9%) of 417 Parkinson's disease (PD) patients with sleepwalking (SW); 72% of them also had a history of REM sleep behaviour disorder (RBD). We aimed to assess the clinical and polysomnographic characteristics of SW in PD and to compare them to patients with PD with and without a history of RBD. Methods: We performed video-polysomnography and detailed clinical examination in 30 PD patients from the above-mentioned survey: 10 patients with a history of SW, 10 patients with a history of RBD, and 10 patients with no history of either SW or RBD. Results: PD patients with SW had higher depression, anxiety and Hoehn Yahr scores and lower activities of daily living scores than patients without a history of RBD but did not differ from patients with RBD. Patients with SW and RBD also had more often dyskinesia and hallucinations. By polysomnography, RBD was observed in 8 patients with SW and in all patients with a history of RBD. A total of 5 patients without a history of either SW or RBD had REM sleep without atonia without behavioural peculiarities. Conclusion: SW in PD is associated with depression, higher disease severity and functional disability. The simultaneous occurrence of SW and RBD (overlap parasomnia) in most patients suggests a common underlying disturbance of motor control during sleep in PD, with variable manifestations in different sleep stages.

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Sleepwalking, REM Sleep Behaviour Disorder and Overlap Parasomnia in Patients with Parkinson's Disease

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Abstract

Background/Aims: In a questionnaire survey we identified 36 (9%) of 417 Parkinson's disease (PD) patients with sleepwalking (SW); 72% of them also had history of REM sleep behaviour disorder (RBD). We aimed to assess the clinical and polysomnographic characteristics of SW in PD and to compare them to patients with PD with and without history of RBD.

Methods: We performed video-polysomnography and detailed clinical examination in 30 PD patients from the above mentioned survey: 10 patients with history of SW, 10 patients with history of RBD and 10 patients with no history of either SW or RBD.

Results: PD patients with SW had higher depression, anxiety and Hoehn and Yahr scores and lower activities of daily living scores than patients without history of RBD but did not differ from patients with RBD. Patients with SW and RBD also had more often dyskinesia and hallucinations. RBD in PSG was observed in eight patients with SW and in all patients with history of RBD. Five patients without history of either SW or RBD had REM sleep without atonia without behavioural peculiarities.

Conclusion: SW in PD is associated with depression, higher disease severity and functional disability. The simultaneous occurrence of SW and RBD (overlap parasomnia) in most patients suggests a common underlying disturbance of motor control during sleep in PD, with variable manifestations in different sleep stages.

Introduction

Parasomnias are defined as undesirable motor phenomena, behaviours, perceptions or emotions that occur predominately during the transition from wakefulness into sleep or arise during arousals from sleep. According to the International Classification of Sleep Disorders (ICSD II) there are three main categories of parasomnias: NREM parasomnias, REM parasomnias and other parasomnias [1]. Sleepwalking (SW) is usually initiated during arousals from slow-wave sleep and presents with complex sleep-associated behaviour. Mental confusion during the episode and amnesia on the next day are common. Injuries and violent behaviours can also be observed [1]. The prevalence of SW in children is about 10% and in adults 2 - 3%, mostly persisting since childhood. Yet adult "de novo" SW is rare and may be observed in only 0.6% [2]. Pathophysiologically, dissociation between motor and mental arousal is suggested. This hypothesis was supported by a study using single-photon emission computed tomography, showing deactivation of the frontoparietal associative cortices and activation of the cingulate cortex without deactivation in thalamus, usually observed in sleep [3]. Polysomnographic findings may indicate an incomplete awakening, although a normal polysomnography recording does not rule out SW.

REM sleep behaviour disorder (RBD) is characterized by loss of the normal muscle atonia that accompanies REM sleep, thus allowing acting out dreams. It is usually associated with jerky, repetitive movements, though more complex behaviours have also been described [4].

RBD has been studied in great detail in patients with Parkinson's disease (PD), yet only a few studies examined NREM parasomnias in PD. An association between SW and PD has been reported in 3 patients in an abstract form [5]. In a retrospective series we found SW in 6 of 165 consecutive patients with PD [6]. Walking in sleep has been reported in PD patients with frequencies ranging from 2.1% to 5.3% [7-9] but detailed characteristics of the phenomenon were not studied. We recently performed a questionnaire based survey specifically asking for SW and its characteristics in PD patients and found an even higher frequency (9%: 36 of 417 patients). Seventy-two percent of these patients also had

history of RBD [10]. Additionally 42.6% of the 417 patients had a history, suggestive of RBD [11]. The present study aimed at assessing the clinical and polysomnographic characteristics of SW in PD and comparing them to patients with PD with and without history of RBD.

Patients and methods

In an earlier study, which was performed in cooperation with the Parkinson's disease patients' organization in Switzerland, we sent a questionnaire examining sleep habits and sleep-wake disorders, especially sleep-related movement disorders such as SW and RBD in PD patients to the members of the organization together with its monthly magazine. A questionnaire on SW and the RBD screening questionnaire (RBDSQ) were included. RBDSQ is a self-assessment tool consisting of 10 items, each requiring a "yes" or "no" answer [12]. A score of 6 or higher on RBDSQ was found to predict RBD in patients with PD [13]. All patients were asked if they had SW in their childhood and/or as adults. The patients who reported SW filled in a more detailed questionnaire on SW with 22 items on frequency of SW, occurrence during the night, recall, awakening during SW, most common and most complex activities during SW, relation of SW behaviour to dreams, injuries, violence, family history and precipitating factors [10]. 417 questionnaires were received back. Based on the history of SW and RBD, responders to the questionnaires were contacted and invited for a detailed clinical examination and overnight video-polysomnography (PSG). Ten PD patients of 36 (5 men and 5 woman with a mean age of 66 ± 11 years, SD) with history of SW (in 4 of them since childhood and in 6 "de novo") agreed to participate in the study. Seven of these 10 patients had RBDSQ scores ≥ 6, suggestive of RBD which corresponds to the overall questionnaire data, where 72% of the patients reporting SW also had RBDSQ scores suggestive of RBD [10]. Additionally patients without history of SW but with RBDSQ scores suggestive of RBD were invited to participate in the study. For this group we selected 10 patients (8 men and 2 women with a mean age of 65 ± 7 years, SD) with high RBDSQ scores (≥10) to increase the possibility of RBD. As a third group 10 patients (5 men and 5 women with mean age of 66 +/- 10 years,

SD) without history of either SW or RBD were included. We selected patients with RBDSQ ≤2 to reduce the possibility of RBD. The diagnosis of PD in all patients was confirmed and fulfilled international criteria [14].

A detailed structured interview assessed sleep habits and sleep-wake disorders, the presence of hallucinations, wearing off symptoms and dyskinesia. Disease severity was judged using the Unified Parkinson's Disease Rating Scale, motor score (UPDRS part III), and the Activities of daily living (ADL) score according to Schwab and England. For cognitive assessment, we performed the mini mental state examination (MMSE). Anxiety and depression were rated using the Beck depression (BDI) and the Beck anxiety inventories (BAI). According to user guidelines scores of 0–9 indicate minimal anxiety or depression, 10–16 mild, 17–29 moderate, and 30–63 severe anxiety or depression [15]. Sleepiness was assessed using the Epworth sleepiness scale (ESS). We also recorded the medical treatment of the patients and calculated the levodopa-equivalent dose as previously reported [16].

All 30 patients underwent standard nocturnal video-PSG consisting of six channel EEG (F3/A2, F4/A1, C3/A2, C4/A1, O1/A2, O2/A1), left and right electrooculography (EOG), submental, left and right anterior tibialis, flexor carpi radialis and adductor digiti minimi electromyography (EMG), electrocardiography (ECG), respiratory flow and effort, and pulse-oximetry. All recordings were done by Medcare Somnologica Studio. Sleep stages and sleep associated events were scored manually according to international criteria [17]. Sleep onset was defined as the first epoch of either NREM 2 or REM sleep. REM sleep scoring of advanced PD patients was performed as previously suggested [18]. For the polysomnographic diagnosis of REM sleep without atonia we monitored not only submental [19] and lower limbs EMG but also upper limbs EMG activity as recently suggested [20].

In addition BAI and BDI questionnaires were sent to all other 26 PD patients with history of SW who were not able to participate in the clinical and polysomnographic study and to 26 patients with no history of either SW or RBD. Fourteen questionnaires from patients with history of SW (11 men and 3

women, with a mean age of 72 ± 7.7 years, SD) and 12 questionnaires from patients without history of either SW or RBD (9 men and 3 women with a mean age of 70.4 ± 7.3 years, SD) were returned.

The study was approved by the local ethics committee (Kantonale Ethikkommission des Kantons Zürich) and all patients signed an informed consent prior to the study.

Statistical analysis was performed using SPSS 18 software. ANOVA with post hoc tests with Bonferroni correction, t-tests and Chi-square tests were used to analyse categorical and continuous variables, respectively. Significance level was set at $p<0.05$.

Results

The clinical characteristics of patients with and without history of SW or RBD are presented in Table 1. Significant differences between the groups were observed for BDI (p=0.01), BAI (p=0.03), H&Y (p=0.022) and ADL scores (p=0.012). Post hoc tests (with Bonferroni correction) revealed that the SW group had higher BDI (p=0.009), BAI (p=0.027) and H&Y scores (p=0.023) and lower ADL scores (p=0.017) than patients without history of RBD but did not differ from patients with history of RBD. Scores indicating moderate or severe depression (scores of 17 or higher) were observed in 5 patients with history of SW and in 3 patients with history of RBD; scores indicating moderate or severe anxiety were observed in 4 patients with history of SW and in 2 patients with history of RBD, none of the patients with no history of RBD and SW had scores of 17 or higher on BDI and BAI.

There were also significant differences in the reported frequency of dyskinesia (p=0.015, reported in six patients with history of RBD, four patients with history of SW and in none of the patients with no history for SW or RBD) and hallucinations (p=0.024, reported in eight patients with history of SW, six patients with history of RBD and in two patients with no history for SW or RBD).

The analysis of the additional BDI and BAI questionnaires received from 14 patients with history of SW and 12 patients without history of either SW or RBD, who did not participate in the clinical and electrophysiological part of the study, revealed even larger differences between patients with history of SW and patients without history of SW or RBD ($p<0.001$ for both scores): BDI (16 ± 9.3 in patients with history of SW, 7 ± 4.7 in patients without history of SW or RBD) and BAI (16.2 ± 9 in patients with history of SW, 7.4 ± 4.5 in patients without history of SW or RBD).

Antiparkinsonian drugs included levodopa (n=30), non-ergot (pramipexole, ropinirole and rotigotine) (n=24), ergot (pergolide) (n=1) dopamine agonists (DA), catechol-ortho-methyl-transferase (COMT) inhibitors (n=12, in seven patients with history of RBD, in three patients with history of SW and in two patients without history of either SW or RBD), amantadine (n=6, in two patients from each group), mono-amino-oxydase-A (MAO-A) inhibitors (n=5, in three patients with history of SW and in two with history of RBD). Mean levodopa equivalent dose was 621.2 ± 582.8 mg in the SW group, 823.0 ± 217.2 mg in the RBD group, and 602.1 ± 425.2 mg in patients with no history of SW or RBD. Other relevant drugs included cholinesterase inhibitors (n=2, in one patient with history of SW and one patient with history of RBD), neuroleptics (n=3, two patient with history of SW and one patient without history of either SW or RBD), benzodiazepines (one patient with RBD), beta-blockers (n=4, one patient with history of SW, one with history of RBD and two without history of either SW or RBD) and antidepressants (n=6, three patients with history of SW were treated with tricyclic antidepressants (TCA), two patients with history of RBD, one with TCA and one with a selective serotonin reuptake inhibitor (SSRI) and one patient without history of either SW or RBD was treated with a serotonin-noradrenaline reuptake inhibitor (SNRI). Two of the patients with history of SW treated with TCA had SW since childhood, in one of them persistent, she did not have RBD in PSG; in the other patient SW ceased in adolescence and recurred with the beginning of the Parkinson's disease symptoms, she also had RBD in PSG. The third patient reported SW and RBD since the beginning of the Parkinson's

disease symptoms and did not associate it with the antidepressive medication. The patient without history of SW or RBD treated with SNRI presented with REM sleep without atonia in PSG.

Quantitative PSG parameters did not differ between the groups (Table 2). As expected in all 10 patients with history highly suggestive of RBD (RBDSQ ≥ 10) the disorder was also confirmed polysomnographically. Eight of 10 patients with history of SW also exhibited RBD in their PSG. Six of them had RBDSQ ≥ 6, suggestive of RBD [13]. In one patient with history of SW and high RBDSQ score RBD could not be confirmed in the PSG. Yet in the original publication of the questionnaire it was stated, that RBDSQ poorly discriminates RBD and SW. Two patients with history of SW and a relatively low score of 4 on RBDSQ demonstrated RBD in their PSG. All patients with history of RBD had not only pronounced twitching and body jerks, but also behavioural peculiarities such as hitting (n=7), vocalisations (n=6), laughing (n=6), gesturing (n=3). In patients with SW and RBD the latter presented not only with excessive twitching and body jerks but also with hitting (n=4), head jerks (n=3), vocalisations (n=3), laughing (n=3) or oral automatisms (n=1). REM sleep without atonia without behavioural peculiarities was observed in five patients without history of either SW or RBD. Sudden arousals from deep NREM sleep were observed in two patients with SW and one patient with RBD.

Discussion

There were three main findings of the present study. First, patients with history of SW and PD scored significantly higher on depression and anxiety questionnaires as compared to PD patients with no history of either SW or RBD. Second, PD patients with history of SW had more advanced disease, higher impairment of activities of daily living and reported more often hallucinations and dyskinesias. Third, polysomnographically RBD was confirmed in eight of 10 PD patients with history of SW (in all six patients with “de novo” SW) and in all 10 patients with history of RBD. However five patients with no history of SW and RBD had REM sleep without atonia. There were no significant differences in any quantitative sleep parameter.

The prevalence of anxiety and depression in PD varies considerably according to different studies due to methodological factors, yet a large body of evidence suggests a higher prevalence of depression in PD in comparison to the general elderly population and to other chronic diseases (e.g. arthritis and diabetes) [21]. A systematic review of patients with PD found that 17% present with major depression, 22% with minor depression, and 13% with dysthymia, whereas clinically relevant depressive symptoms were present in 35% of patients with PD [22]. Additionally a higher frequency of SW in depressed patients has been observed [23]. NREM abnormalities have been shown in depressed subjects with a shift of the slow wave delta activity to the initial part of the sleep period following psychotherapy. Subjects who experienced recurrence of depression showed less baseline slow wave activity, compared to those in remission after 1 year [24]. It has been hypothesized that NREM sleep abnormalities in depression might predispose to dysfunctional transitions between sleep and wakefulness, particularly in the early part of the sleep period [25]. Thus there is some evidence for an association between depression and SW. Furthermore a number of drugs have been reported to occasionally induce SW: hypnotics, antipsychotics, antihistaminics, alcohol and especially antidepressants, including SSRI [26-28]. Serotonin neurons originating from the dorsal raphe nucleus project to the cholinergic laterodorsal and pedunculopontine tegmental areas, inhibiting “REM-on” neurons and therefore inhibiting REM sleep [29]. SSRI, TCA (also through anticholinergic effects leading to reduced cholinergic atonia in REM sleep) and SNRI have all been found to increase the occurrence of both REM and NREM parasomnias [23]. Patients on serotonergic antidepressants exhibited increased submental EMG during REM sleep so an effect of serotonin on motor systems at the spinal cord or brainstem level as a possible mechanism has been suggested [30]. Thus serotonin (5-HT) has been implicated on one hand in the regulation of sleep-wakefulness and motor control during sleep and on the other hand in the pathophysiology of RBD and SW [31] as well as depression, including depression in PD [32-34]. Politis et al. found that depressive symptoms in PD patients correlate with higher serotonin transporter (5-HTT) binding in raphe nuclei and limbic structures, possibly reflecting lower extracellular serotonin levels [33]. Using the loudness dependence of auditory evoked potentials, an indicator of central

serotonergic function, Buecke et al. suggested lower serotonergic activity in PD and assumed, that this could be related to high prevalence of depression in PD [32]. The serotoninergic hypothesis of SW postulates that dissociated activity of serotonergic neurons of the raphe nuclei of the brainstem and the serotonergic neurons which modulate the motor system may result in SW. These two neuronal systems are normally coordinated so that increased arousal leads to increased motor activity, but when the two systems dissociate, sleepwalking can result [26,31]. It is therefore conceivable that serotonergic dysfunction in depression and PD influences sleep-wakefulness regulation and motor control during both REM and NREM sleep and could possibly trigger RBD and SW. Indeed our patients with PD and history of SW, eight of whom also had polysomnographically confirmed RBD, had significantly higher scores for depression and anxiety in comparison to patients without history of either SW or RBD.

In line with the findings of longer disease duration [35] and higher disease severity [36] in depressed patients with PD, our PD patients with history of SW also suffered from more advanced disease (as measured by the H&Y stage score) and higher functional disability. The higher frequency of dyskinesias and hallucinations in these patients also suggest a more advanced disease. The presence of levodopa-induced dyskinesias is correlated with an increased incidence of depression [37].

Hallucinations have been linked to cognitive impairment in PD [38]. Furthermore night-time wandering behaviour has been reported in male PD patients with cognitive decline, living in nursing homes [39]. However, using MMS we did not find significant differences between PD patients with history of SW, RBD and no history of either of the two. On one hand hallucination can simply arise from a more advanced disease [38,40]. On the other hand similar neurodegenerative changes in brainstem and limbic structures may underlie both visual hallucinations (VH) and SW in PD [40]. Recently, increased 5HT-2_A receptor binding in the ventral visual pathway has been reported in PD patients with VH [41]. Thus 5-HT can be implicated not only in the pathophysiology of SW and depression in PD but also in hallucinations.

Quantitative polysomnographic parameters did not differ between PD patients with history of SW, PD with history of RBD and PD without history of either SW or RBD. It should however be stressed, that

diagnosis of SW was based on history. In PSG episodes suggestive of SW (sudden arousals from NREM sleep) were observed in two patients with history of SW. No ambulatory behaviour was observed during sleep. Yet according to ICSD 2 [1] polysomnographic confirmation does not belong to the diagnostic criteria of SW. As we have previously discussed, we cannot rule out that SW represents a severe manifestation of RBD and is therefore present in only a small number of patients with RBD. According to the ICSD II [1] RBD is defined by the following criteria: a) presence of REM sleep without atonia: the EMG finding of excessive amounts of sustained or intermittent elevation of submental EMG tone or excessive phasic submental or (upper or lower) limb EMG twitching; b) at least one of the following: i. sleep related injurious, potentially injurious, or or disruptive behaviours by history; ii. abnormal REM sleep behaviours documented during polysomnographic monitoring; c) absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep related seizure disorder; and d) the sleep disorder is not better explained by another sleep disorder, medical or neurological disorder, mental disorder medication use, or substance use disorder. Restoration of motor control in PD during REM sleep has been hypothesized [42] which would facilitate ambulatory activity. Getting out of bed and walking as a representation of RBD, has been reported in a few series of patients with idiopathic and symptomatic RBD [43,44]. One could argue if an item should be added to RBDSQ to include ambulatory behaviour as a part of RBD. However SW has not been documented with PSG to arise from REM sleep. In detailed analysis of 100 patients with PD and history of RBD, SW was observed in only one patient in whom RBD could not be demonstrated with PSG [42]. RBD could be polysomnographically confirmed in 8/10 PD patients with SW (in all 6 patients with SW “de novo”). This is rather in favour of our hypothesis of a common underlying disturbance of motor control during sleep in PD, with variable manifestations according to different sleep stages [10].

However REM sleep without atonia could be polysomnographically confirmed in five patients with no history of sleep-related movement disorders. These patients presented with twitching and occasional

body jerks (in five out of five), while all patients with history for RBD and RBD and SW showed also behavioural peculiarities. This suggests a milder or beginning form of RBD and probably lesser or no night-time impairment in patients with no history of RBD.

Limitations of the present study include the small sample size and the lack of a healthy control group. We also have to note that six patients were treated with antidepressants which are reported to increase the frequency of REM and NREM parasomnias. Two of these patients had SW since childhood so antidepressive therapy could not have caused their SW episodes, yet it could have precipitated their occurrence. We could not exclude patients on andidepressants as we were limited in our choice of patients to the results of the previously performed questionnaire study [10] and the consent of the patients to participate in the clinical and elecrophysiological part of the study. Additionally MMS is only a screening tool and provides only limited information about cognitive impairment in PD. As we had only two patients with history of SW and no polysomnographically confirmed RBD we could not compare patients with SW only and patients with both SW and RBD. This issue should be addressed by further studies. Yet all patients in each group were characterized clinically and electrophysiologically in detail.

Conclusion

SW in PD is associated with depression, higher disease severity and higher functional disability. The simultaneous occurrence of SW and RBD (overlap parasomnia) in most patients suggests a common underlying disturbance of motor control during sleep in PD, with variable manifestations according to different sleep stages. It can also be speculated, that serotonin dysfunction might be the link between ambulatory behaviour during sleep, depression and hallucinations in PD.

All authors declare no conflict of interest.

Disclosures:

Ms Di Fabio, Dr. Poryazova and Dr. Oberholzer have nothing to disclose

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Table 1: Demographic and clinical characteristics of patients with Parkinson's disease with and without history of SW or RBD.

	SW (n=10) mean ± SD	RBD (n=10) mean ± SD	no SW or RBD (n=10) mean ± SD	p
Age, y	66 (11.6)	65.5 (7.3)	65.8 (9.7)	ns
Sex, % men	50	80	50	ns
Disease duration, y	12.3 (9.1)	11.5 (5.3)	8.2 (6.9)	ns
Therapy duration, y	11.1 (8.9)	9.8 (5.0)	7 (6.7)	ns
LDE, mg/day	671.2 (582.8)	823.0 (217.2)	602.1 (425.2)	ns
UPDRS, part III	26.5 (14.6)	22.1 (9.8)	18.0 (8.0)	ns
RBDSQ score	7.0 (2.7)	11.3 (0.9)	1.4 (0.5)	
MMSE	27.1 (3.0)	28.7 (1.7)	27.7 (3.3)	ns
BDI	14.6 (6.3)	11.4 (6.4)	6.2 (3.6)	0.01
BAI	15 (7.9)	10.4 (7.1)	6.6 (4.0)	0.03
Hoehn und Yahr score	3.1 (0.74)	2.5 (0.77)	2.2 (0.59)	0.022
Schwab & England score	64 (21.7)	81.0 (12.9)	84 (5.2)	0.012
ESS	14.4 (4.6)	9.90 (4.0)	10.8 (5.8)	ns

BDI and BAI - Beck Depression and Anxiety Inventory; ESS - Epworth Sleepiness Scale; LDE - Levodopa-equivalent dose; MMSE - Mini Mental State Examination; RBD - REM sleep behaviour disorder screening questionnaire; UPDRS, part III - Unified Parkinson's Disease Rating Scale.

Table 2: Sleep measures in patients with Parkinson's disease with and without history of SW or RBD

	SW (n=10) mean ± SD	RBD (n=10) mean ± SD	no SW or RBD (n=10) mean ± SD	p
Latency to, min				
Sleep onset	36.4 (65.8)	47.4 (89.9)	22.4 (12.7)	ns
REM sleep	131.3 (81.8)	167.9 (103.4)	152.3 (75.0)	ns
TST, min	336.8 (138.1)	332.0 (107.6)	338.1 (62.4)	ns
Sleep duration, % TST				
Wake	24.1 (24.6)	27.5 (19.2)	27.4 (13.4)	ns
NREM1	16.0 (10.2)	10.8 (6.3)	14.0 (5.1)	ns
NREM2	35.2 (20.0)	32.1 (11.9)	32.2 (8.5)	ns
Slow wave sleep	12.8 (11.7)	12.3 (6.5)	15.9 (8.5)	ns
REM	12.0 (7.3)	16.3 (8.3)	10.5 (4.7)	ns
Sleep efficiency	75.9 (24.6)	72.5 (19.2)	72.6 (13.4)	ns
Arousal index	10.5 (10.0)	7.5 (3.7)	13.5 (5.4)	ns
AHI	8.1 (11.7)	10.3 (11.2)	14.9 (13.7)	ns
PLMS	7.0 (12.6)	2.6 (5.0)	17.3 (32.8)	ns

AHI – apnea/hypopnea index; PLMS – periodic limb movements in sleep; TST – total sleep time.